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November 17, 2003

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APPLICATION NUMBER: ***60/417,460***
FILING DATE: ***October 10, 2002***

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Certifying Officer

10-18-02 A PROV

Practitioner's Docket No. U014254-3 ***PATENT***

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: AMIR ARAV

For: METHOD AND SYSTEM FOR CONTROLLING THE BIOLOGICAL SAMPLES DEVELOPMENT

Box Provisional Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231

Optional Customer No. Bar Code

00140
PATENT TRADEMARK OFFICE

COVER SHEET FOR FILING PROVISIONAL APPLICATION (37 C.F.R. § 1.51(c)(1))

WARNING: *"A provisional application must also include the cover sheet required by § 1.51(c)(1) or a cover letter identifying the application as a provisional application. Otherwise, the application will be treated as an application filed under paragraph (b) [nonprovisional application] of this section " 37 C.F.R § 1.53(c)(1).. See also M.P.E.P. § 201.04(b), 6th ed., rev. 3.*

CERTIFICATION UNDER 37 C.F.R. 1.10*
(Express Mail label number is mandatory.)
(Express Mail certification is optional.)

I hereby certify that this correspondence and the documents referred to as attached therein are being deposited with the United States Postal Service on October 10, 2002 (date), in an envelope as "EXPRESS MAIL POST OFFICE TO ADDRESSEE" service under 37 C.F.R. 1.10 Mailing Label Number EV011024780US addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

SUE DARGENIO
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WARNING: *Certificate of mailing (first class) or facsimile transmission procedures of 37 C.F.R. 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence.*

**WARNING:* *Each paper or fee filed by "Express Mail" must have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. 1.10(b).*

"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will not be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.

NOTE: "A complete provisional application does not require claims since no examination on the merits will be given to a provisional application. However, provisional applications may be filed with one or more claims as part of the application. Nevertheless, no additional claim fee or multiple dependent claims fee will be required in a provisional application." Notice of December 5, 1994, 59 FR 63951, at 63953.

"Any claim filed with a provisional application will, of course, be considered part of the original provisional application disclosure." Notice of April 14, 1995, 60 Fed. Reg. 20,195, at 20,209.

NOTE: "A provisional application is not entitled to the right of priority under 35 U.S.C. 119 or 365(a) or § 1.55, or to the benefit of an earlier filing date under 35 U.S.C. 120, 121 or 365(c) or § 1.78 of any other application. No claim for priority under § 1.78(a)(3) may be made in a design application based on a provisional application No request under § 1.293 for a statutory invention registration may be filed in a provisional application. The requirements of §§ 1.821 through 1.825 regarding application disclosures containing nucleotide and/or amino acid sequences are not mandatory for provisional applications." 37 C.F.R. 1.53(c)(3).

NOTE: "No information disclosure statement may be filed in a provisional application." 37 C.F.R. § 1.51(d). "Any information disclosure statements filed in a provisional application would either be returned or disposed of at the convenience of the Office." Notice of December 5, 1994, 59 FR 63591, at 63594.

NOTE: "No amendment other than to make the provisional application comply with the patent statute and all applicable regulations, may be made to the provisional application after the filing date of the provisional application. " 37 C.F.R. § 1.53(c)

NOTE: 35 U.S.C. 119(e) provides that "[i]f the day that is 12 months after the filing date of a provisional application falls on a Saturday, Sunday, or Federal Holiday within the District of Columbia, the period of pendency of the provisional application shall be extended to the next succeeding secular or business day."

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 C.F.R. § 1.51(c)(1)(i).

1. The following comprises the information required by 37 C.F.R. § 1.51(c)(1):

2. The name(s) of the inventor(s) is/are (37 C.F.R. § 1.51(c)(1)(ii)):

NOTE: "If the correct inventor or inventors are not named on filing, a provisional application without a cover sheet under § 1.51(c)(1), the later submission of a cover sheet under § 1.51(c)(1) during the pendency of the application will act to correct the earlier identification of inventorship." 37 C.F.R § 1.48(f)(2)

NOTE: "The naming of inventors for obtaining a filing date for a provisional application is the same as for other applications. A provisional application filed with the inventors identified as 'Jones et al.' will not be accorded a filing date earlier than the date upon which the name of each inventor is supplied unless a petition with the fee set forth in § 1.17(i) is filed which sets forth the reasons the delay in supplying the names should be excused. Administrative oversight is an acceptable reason. It should be noted that for a 35 U.S.C. 111(a) application to be entitled to claim the benefit of the filing date of a provisional application the 35 U.S.C. 111(a)[,] application must have at least one inventor in common with the provisional application." Notice of April 14, 1995, 60 Fed. Reg. 20,195, at 20,209.

The term "invention" is typically used to refer to subject matter which applicant is claiming in his/her application. Because claims are not required in a provisional application, it would not be appropriate to reference joint inventors as those who have made a contribution to the "invention" disclosed in the provisional application. If the "invention" has not been determined in the provisional application because no claims have been presented, then the name(s) of those person(s) who have made a contribution to the subject matter disclosed in the provisional application should be submitted. Section 1.45(c) states that "if multiple inventors are named in a provisional application, each named inventor must have made a contribution, individually or jointly, to the subject matter disclosed in the provisional application." All that § 1.45(c) requires is that if someone is named as an inventor, that person must have made a contribution to the subject matter disclosed in the provisional application. When applicant has determined what the invention is by the filing of the 35 U.S.C. 111(a) application, that is the time when the correct inventors must be named. The 35 U.S.C. 111(a) application must have an inventor in common with the provisional application in order for the 35 U.S.C. 111(a) application to be entitled to claim the benefit of the provisional application under 35 U.S.C. 119(e). Notice of April 14, 1995, 60 Fed. Reg. 20,195, at 20,208.

See 37 C.F.R. § 1.53.

	GIVEN NAME	MIDDLE INITIAL OR NAME	FAMILY (OR LAST) NAME
1.	AMIR		ARAV
2.			
3.			

3. Residence address(es) of the inventor(s), as numbered above (37 C.F.R. § 1.51(c)(1)(iii)):

1. BEIT DAGAN, ISRAEL

2.

3.

4. The title of the invention is (37 C.F.R. § 1.51(c)(1)(iv)):
METHOD AND SYSTEM FOR CONTROLLING THE BIOLOGICAL SAMPLES DEVELOPMENT

5. The name, registration, customer and telephone numbers of the practitioner *(if applicable)* are (37 C.F.R. § 1.51(c)(1)(v)):

Name of practitioner: WILLIAM R. EVANS
Reg. No. 25,858 Tel. (212) 708-1930
Customer No. 00140

(complete the following, if applicable)

[ ] A power of attorney accompanies this cover sheet.

6. The docket number used to identify this application is (37 C.F.R. § 1.51(c)(1)(vi)):

Docket No. U014254-3

7. The correspondence address for this application is (37 C.F.R. § 1.51(c)(1)(vii)):

Ladas & Parry, 26 West 61st Street, New York, NY 10023

8. Statement as to whether invention was made by an agency of the U.S. Government or under contract with an agency of the U.S. Government. (37 C.F.R. § 1.51(c)(1)(viii)).

This invention was made by an agency of the United States Government, or under contract with an agency of the United States Government.

[X] No
[ ] Yes

The name of the U.S. Government agency and the Government contract number are:

_____

_____

9. Identification of documents accompanying this cover sheet:

A. Documents required by 37 C.F.R. §§ 1.51(c)(2)-(3):

Specification: No. of pages 28
Drawings: No. of sheets 4

B. Additional documents:

[ ] Claims: No. of claims _____

Note: See 37 C.F.R. § 1.51.

[ ] Power of attorney
[X] Small Entity Statement or Written Assertion
[ ] Assignment
[ ] English language translation of non-English provisional application

NOTE: A provisional application which is filed in a language other than English, does not have to have an English language translation. See 37 C.F.R. § 1.52(d)(2). However, if the provisional application is not in the English language and will later serve as a benefit of its filing date for a nonprovisional application, other than a design patent, or for an international application designating the U.S., then an English language translation must be filed in the provisional application or the later filed nonprovisional application. See § 1.78(a)(5)(iv).

[ ] This application is in a language other than English and an English translation along with a statement of its accuracy is submitted herewith.

[ ] Other

10. Fee

The filing fee for this provisional application, as set in 37 C.F.R. § 1.16(k), is $160.00, for other than a small entity, and $80.00, for a small entity.

[ ] Applicant is not a small entity.
[X] Applicant is a small entity.

NOTE: "A . . . statement i compliance with existing § 1.27 is required to be filed in each provisional application in which it is desired to pay reduced fees." Notice of April 14, 1995, 60 Fed. Reg. 20, 195, at 20,197.

11. Small entity assertion

[X] The assertion that this is a filing by a small entity under 37 C.F.R. § 1.27(c)(1) is attached. ("ASSERTION OF SMALL ENTITY STATUS")

[ ] Small entity status is asserted for this application by payment of the small entity filing fee under § 1.16(k). 37 C.F.R. § 1.27(c)(3).

WARNING: "Small entity status must not be established unless the person or persons signing the . . . statement can unequivocally make the required self-certification." M P.E.P. Section 509 03, 6th ed., rev. 2, July 1996 (emphasis added)

12. Fee payment

[X] Fee payment in the amount of $ 80.00 is being made at this time.

[ ] No filing fee is to be paid at this time. (This and the surcharge required by 37 C.F.R. § 1.16(l) can be paid subsequently.)

13. Method of fee payment

[X] Check in the amount of $ 80.00 .
[ ] Charge Account No. 12-0425 , in the amount of $ _____.
A duplicate of this Cover Sheet is attached.

Please charge Account No. 12-0425 for any fee deficiency.

Date: _____

_____
Signature of submitter

Tel.: ( )

OR

Date: October 10, 2002

_____
Signature of practitioner

Reg. No.: 25,858

WILLIAM R. EVANS
(type or print name of practitioner)

Tel.: (212) 708-1930

_____
P.O. Address

Customer No.: 00140

c/o Ladas & Parry
26 West 61st Street
New York, N.Y. 10023

METHOD AND SYSTEM FOR CONTROLLING THE BIOLOGICAL SAMPLES DEVELOPMENT

FIELD OF THE INVENTION

This invention relates in general to monitoring and control of biological samples during their development as well as to their preservation. The invention is particularly useful for monitoring and controlling the samples development during Assisted Reproductive Technologies (ART)

BACKGROUND OF THE INVENTION

In the filed of cyropreservation and reproduction of biological samples many techniques and supporting technologies, including microscope monitoring have been and still are under development. As microscope is the basic tool for most biological procedures, it is very commonly used in biology. In every laboratory there are usually several types of microscopes and most of the devices have a special adapter for video or CCD camera. However, this simple approach has several limitations.

One improvement of the basic microscope technology is described in US 6,166,761, providing a method an apparatus, which avoids the need for a microscope. Very small CCD or video cameras, with special adapters and microscopic lenses are provided to produce high quality imaging of biological samples in an incubator.

Embryo development is on example of a biological sample for monitoring and control during ART, by the use of the different cyropreservation and reproduction technologies under development.

Infertility problems and treatment thereof is a growing area of health care. Many approaches are being developed to resolve problems with infertility. Infertility is understood to be the inability to conceive after six to twelve months of sexual activity without the use of contraceptives, depending on the age of the persons involved. Because infertility exerts extreme physical, emotional and financial stresses on those who are unable to conceive, there is a great need for improved aids for reproduction. By far the most common ART component is *In Vitro* Fertilization (IVF), which has grown explosively in the two decades since it was developed. In its simplest form, IVF consists of pharmaceutical stimulation of the female's ovaries to produce a large number of follicles. Eggs surgically harvested from these follicles are then mixed in the laboratory with the male's sperm. If fertilization is successful, the embryos are incubated for a short time and then transferred back to the female. If one of these embryos implants in the uterine wall, a successful pregnancy may follow.

There are several modifications of this basic technique. For example, intracytoplasmic sperm injection (ICSI) can be used for cases of low sperm count or cases where the sperm has difficulty fertilizing the egg. Another IVF modification is Assisted Hatching (AH), a procedure in which the zona pellucida (the outer wall of the embryo) is mechanically cut or chemically etched, thereby partially exposing the embryo. In some laboratories, this procedure significantly improves implantation rates, particularly for older patients. Finally, IVF procedures can also incorporate donor tissues, including sperm, ova and embryos, for those individuals who cannot produce their own.

Despite its great successes, IVF has several significant problems. First and foremost, the procedure is unpredictable. Although the ideal result of any IVF procedure is a single, live birth, a viable pregnancy occurs in only about 30% of all procedures. Conversely, IVF may result in a pregnancy with multiple

embryos. In this regard, twins and triplets pose relatively few risks beyond a single embryo pregnancy. The potential for problems, however, increases for higher order births. Selective embryo reduction is therefore often recommended for these cases.

IVF begins with a source of sperm and oocyte. There is a virtually 100% certainty of obtaining these materials, using donor tissues if necessary. Next, fertilization occurs, and good IVF laboratories typically have a fertilization success rate of about 75%, using ICSI if appropriate. After a short incubation period, the resulting embryo is then introduced into the uterus, where implantation occurs.

Implantation is generally the limiting factor in overall IVF success. Implantation itself consists of several steps. First, the embryo must enter the uterine cavity. In normal reproduction, without ART, the embryo descends through the fallopian tubes. The embryo then comes into contact with some point on the uterine wall. Next, the embryo and wall surfaces fuse at the contact point. The uterine wall properties then change dramatically at the implantation site, thus allowing the embryo to become fully implanted. For IVF, the embryo is carried into the uterine cavity in a solution injected from a syringe inserted through the cervical canal.

Although the implantation process appears to be simple enough, it is actually quite complicated and requires the coordination of many factors, some of which are unknown. A failure of any one of these processes prevents implantation and thus pregnancy.

Currently, monitoring procedure of embryos is done manually, by taking the embryos out of the incubator, placing them under a microscope and investigating their development. However, this approach has several limitations that may result in damage to the embryos. To assure the best conditions for embryo development it is essential that the embryos remain in a stable controlled environment.

In addition, during ART procedures special attention is paid to the issue of

matching between oocytes and sperms or embryos and patient. Even a minor mistake could lead to a personal disaster for the future parents. Only recently, an IVF mix-up occurred where black twins were born to a white couple (http://news.bbc.co.uk/1/hi/health/211552.stm). This blunder thus emphasizes the need in IFV procedures for carefully monitoring the processing of the oocyte and sperm during the entire ART procedures.

SUMMARY OF THE INVENTION

There is a need in the art to facilitate monitoring and controlling of biological samples development by providing a novel optical method and system.

The main idea of the present invention consists of providing monitoring and controlling of the biological samples development and IVF, while in an incubator. Incubator is known as closed environment for maintaining a biological samples' equipped with the standard environment control means, such as temperature and humidity control means, CO_2 and oxygen levels' control means, aseptic environment control means, etc. One example of an incubator which may be utilized in the method and system of the present invention is described in US 6,166,761, incorporated herein by reverence.

The present invention provides a method and system enabling continuous monitoring and controlling of biological samples during their development in the incubator and during the IVF. By the method and system of the present invention, it is possible to retain the biological sample under a stable controlled environment. Therefore, the typical procedure of taking a biological sample, such as an embryo, out of an incubator for monitor under a microscope is avoided.

As appreciated, taking a biological sample out of the incubator may harm the development of the sample and, at times, there is a need to monitor the development of the sample at predefined time-laps during the development process, e.g. every three hours (such as in the case of embryo development), which greatly increases the risk of harming the biological sample. Yet further, using a microscope for monitoring the biological sample outside the incubator requires that the

biological sample be contained in a special solution (oil), which may damage the sample.

The present invention aims for providing a method and system for the continuous monitoring of samples, in particular, embryos, without the need to take the sample out of the incubator.

Moreover, the present invention provides means for ensuring matching between at least two biological entities, e.g., biological samples (sperm sample, oocytes sample, embryo sample, blood sample, bone marrow sample, bacteria/antibiotic samples, drug or other agents sample), donor subjects, recipients, etc. To this end, the present invention utilizes a unique identification code (e.g., barcode), which is associated with the specific biological sample or a specific set of biological samples, and is identifiable through processing an image of the ID carrier, and sometimes concurrent processing of the image of the biological sample and its ID. This is achieved by enabling location of the barcode and the associated biological samples (together with their additional identification marks if any) within the imaging plane.

When a specific set of biological samples is assigned with the same unique identification code or matching identification codes, the invention provides for concurrent identification of the biological samples to enable matching therebetween. The invention thereby prevents mix-up of biological samples.

According to one aspect of the invention, there is provides a system and method for monitoring of embryo development. This aspect is referred to hereinafter as the "*the embryo development embodiment*". According to this embodiment, the system and method of the invention automatically monitors each embryo at predefined time-laps during development (e.g., every three hours) and stores this data, for example, as image files. It should be appreciated that the image files may be in the form of a single frame image or of continuous frames (e.g. a short video film). Each sample has its unique record (referred to as the "embryo record"). The system utilizes a modified incubator additionally equipped with optical, robotic and control means of the present invention. The optical means

includes at least one image acquisition system utilizing magnification optics (e.g., microscopic lens arrangement). The control means includes an external control system that is typically a computer system installed with specific utilities (hardware and software) and utilizes an image processing technique based on pattern recognition. The robotic means is operable by the control means and includes a sample positioning assembly for locating a selected one of the samples within an imaging plane. The system may also comprise a catheter/pipette for inserting required solutions into the sample drops to thereby control the media environment thereof, and/or may comprise a laser-assisted etcher for assisted hatching of the embryo.

According to another aspect, the invention provides a system and method for controlling a process of biological entities matching. This in implemented by using a holder for each of the biological entities labeled with a unique identification code assigned to the respective biological entity, and a matcher device. The latter has a support platform for supporting the labeled holders, and an imaging arrangement operable to acquire images of the labels and generate data indicative thereof. The previously created records representative of matching sets of biological entities' identification codes are used for analyzing the image generated data to identify the identification codes and determine whether the respective biological entities belong to a matching set.

BRIEF DESCRIPTION OF THE DRAWINGS

In order to understand the invention and to see how it may be carried out in practice, preferred embodiments will now be described, by way of non-limiting example only, with reference to the accompanying drawings, in which:

Fig. 1 illustrates biological samples' holders according to the invention;

Fig. 2 is a schematic illustration of a matcher device according to the invention;

Fig. 3 is a schematic illustration of an incubator equipped with a system according to the invention (*"embryo-guard unit"*);

Fig. 4 is a schematic illustration of a medium changer assembly for maintaining controlled environment within a sample drop;

Fig. 5 exemplifies the evaluation scheme obtained while monitoring embryos in the embryo-guard unit and used for selecting the best embryo for implantation; and

Fig. 6 illustrates a flow diagram of the operational steps in the entire method of monitoring and controlling an IVF process including the operation of the matcher device and the embryo-guard unit.

DETAILED DESCRIPTION OF THE INVENTION

More specifically, the present invention is used for monitoring and controlling of ART (such as IVF) and is therefore described below with respect to this specific application. It should, however, be understood that the invention may be useful for other applications dealing with biological samples handling.

Referring to **Fig. 1**, there are illustrated two holders $\mathbf{H_1}$ and $\mathbf{H_2}$ containing a matching pair of oocyte and sperm samples, respectively, which are to be involved in a common fertilization process. The holder $\mathbf{H_1}$ is shaped like a dish or plate for carrying oocytes samples. Such a dish is generally known and widely used in biological samples inspection processes, and therefore need not be more specifically described. According to the invention, the dish $\mathbf{H_1}$ at its outer surface carries a label **10** that includes a unique identification code ID_1 (e.g., barcode) assigned to the specific female, to whom the specific oocyte samples belong, and has a pattern defining a certain number of spaced-apart sites (12 such sites in the present example) each for carrying one of the samples (sample drop containing a single oocyte). The sites are assigned with identification marks (numbers) 1,..., 12. The pattern may be in the form of a plurality of spaced-apart holes. Generally, at least the pattern elements (sites) of the label, and preferably the entire label region on which the ID is printed, are transparent with respect to predetermined radiation. The holder $\mathbf{H_1}$ is preferably formed with a projecting portion **12** that serves for assisting in attaching the label to the dish surface. The portion **12** is preferably

formed with a marker **M** (black line) for assisting alignment of the dish-with-label during further procedures. The other holder $\mathbf{H_2}$ is preferably shaped like a tube, and is also attached with a label including an identification code ID_2, which may and may not be identical to ID_1, but is that previously recorded as matching with ID_1. In other words, the codes ID_1 and ID_2 present a matching set.

The label may be attached to the dish by electrostatic means, by using organic glues (such as fibrinogen derived materials) or any other means, which do not influence or damage the sample in the dish.

The provision of such matching labels (i.e., labels with matching IDs) on the pair of holders of biological samples to be paired, allows for automatic authentication of two holders arriving to a fertilization stage.

Fig. 2 illustrates a matcher device **20** according to the invention. The matcher device **20** comprises a temperature and/or gas-controlled platform **22** (e.g., temperature of 37°C and/or oxygen level control) for supporting the holders $\mathbf{H_1}$ and $\mathbf{H_2}$, an imaging means **24**, and a control unit **26** connectable to the imaging means (through wires or wireless). In the present example, the imaging means comprises two imaging systems $\mathbf{IS_1}$ and $\mathbf{IS_2}$ for capturing images of the biological samples in holders $\mathbf{H_1}$ and $\mathbf{H_2}$, respectively. These imaging systems utilize a common or separate light sources generating radiation of a spectral range and exposure time causing no damage to biological samples (such damage typically including peroxidation of the cells' lipids)(typically excluding UV and IR). The entire system $\mathbf{IS_1}$ or at least its light source may be located below the dish (the so-called "back Illumination" mode), in which case the platform would be transparent or be of a frame-like design allowing back illuminated light propagation to the dish $\mathbf{H_1}$.

Each imaging system comprises its own lens arrangement and optical detector. Such an imaging system may be a digital or video camera. It should be understood that, generally, a single imaging system (digital or video camera) could be used for the same purposes, by sequentially capturing images of the sample-with-label in two holders. As for reading the corresponding identification codes

attached to the patients involved in this specific IVF procedure, a portable barcode scanner can be used.

The control unit **22** operates the imaging systems IS_1 and IS_2 for substantially simultaneous imaging the IDs and to analyze the images to determine whether the IDs match each other or not, and generate a signal indicative thereof. The control unit **22** is a computer system preprogrammed with suitable software for carrying out pattern recognition based image processing, and utilizing a database where the matching ID sets are previously recorded.

Fig. 3 schematically illustrates an incubator **30** equipped with a system **32** according to the invention (referred to as *"embryo-guard unit"*). The system **32** comprises an optical arrangement **34** and a sample positioning stage **36** located inside the incubator **30**, and an external control system **38**.

To facilitate illustration, all the conventional elements of the incubator (such as temperature, humidity, CO_2 and oxygen levels, light and other control means) known *per se* are not shown here. Generally speaking, the incubator is designed and operated to maintain the following environmental conditions: substantially steady temperature of 38°C; a CO_2 level of 5%, oxygen level between 5 to 25%, a 100% relative humidity, substantially dark and sterilized environment.

The positioning stage **36** serves for supporting a plurality of embryos containing dishes H_1, ... H_N. The system therefore enables concurrent monitoring and controlling of multiple patients' samples within one embryo-guard unit. The dishes are arranged in a circular array, and the stage **36** is rotatable so as to bring each one of the dishes to an imaging position with respect to the optical arrangement **34**.

The optical arrangement **34** is an imaging system (camera) including a light source arrangement, a lens arrangement, and a light detection arrangement. The construction and operation of all these elements are known *per se* and are therefore not specifically shown and described, except to note the following. A light emitting unit of the light source arrangement may be located inside the incubator, or outside thereof in which case emitted light is directed towards the inside of the incubator

via fiber(s). the light may be of any source, a short exposure of the embryo to which does not damage the latter. Such light sources include visible light, infrared light, ultraviolet light and others.

The system **32** is intended for monitoring the samples inside the incubator for the purpose of evaluating development of the embryos, and eventually selecting the most suitable embryo for each subject (patient) for further implantation in the uterine wall. To this end, imaging of the samples, as well as samples' identification, are to be carried out. Generally, the imaging procedure includes the following: simultaneous imaging of the entire dish (all the sample drops in the dish and the ID/identification marks), imaging of the sample drop only, and imaging of the embryo within the drop. These three image acquisition procedures practically need different magnification optics, and therefore can be implemented by three different imaging systems having different image magnification factors and/or fields of view, or by the same imaging system with changeable lens arrangements. For example, for imaging the entire dish-with-label a magnification factor of 1-2 is used, for imaging the specific sample drop a magnification factor of 2-6 is used, and for imaging the embryo within the sample drop a magnification factor of 10-100 is used. The imaging system is also preferably equipped with an auto-focus arrangement.

It should be noted, although not specifically shown, that the system **32** preferably also contains means for carrying out a fertilization stage. Such means may include a zona drilling tool which assists fertilization, or a micromanipulation tool, such as that used in a fertilization process known as intracytoplasmic sperm injection (ICSI). These processes may be automatically operated by displacing (rotating) either the stage **36** or the tool to bring the tool to a respective position with respect to a selected sample. It should, however, be noted that the fertilization may be performed outside the system **32**, as well as may be done by using of a standard samples' mixing procedure, in which case it is preferably carried out automatically: a portion of the sperm sample is automatically brought in contact with an oocyte sample drop. If the fertilization is carried out inside the incubator

equipped with the system **32** of the present invention, the same optical arrangement **34** is used for imaging the fertilized oocyte sample and recording the sample-with-ID_i image. At times, the fertilized oocyte sample may be assigned with another ID associated with said ID_i matching set.

Further preferably provided in the system **32** is a medium changer assembly **40** shown in **Fig. 4**. The medium changer assembly **40** is aimed at maintaining controlled environment within the sample drop **SD** (located in a selected site of the dish). The medium changer **40** is typically in the form of a catheter or pipette for adding the required medium into the sample drop such as cleavage medium or blastocyst medium. The medium to be provided to the embryo is typically kept at low temperature, e.g. 4°C and is warmed (e.g. to a temperature of 37°C) and gazed before use. The medium changer may also be employed for fertilization or for exposing the embryo to other suitable agents (in example, cryoprotectants or dyes).

The system **32** may operate as follows: The stage **36** is periodically actuated for rotation, e.g., every three hours, and during the rotation cycle, the sample dishes are successively brought to the imaging position with respect to the camera(s) **34**. The control system **38** is preferably equipped with a specific electronic card for controlling the movement of the stage. The cameras (or a single camera with changeable lenses) are operated to acquire three images within the respective dish as described above, wherein for imaging of the embryo within the sample drop, the camera is moved with respect to the stationer sample drop. The control system **38** may for example utilize the RS 232 composite video channel or USB protocol/connection for inputting the image related data coming from the camera into a frame grabber card. The magnification factor between the image related data coming from the camera (CCD) and a control system monitor may for example be about 20. The magnification can be carried out by suitable digital means. In a specific example, the entire dish appears on the monitor with a 54mm diameter, the sample drop appears on the monitor with a 5mm diameter, and the embryo appears on the monitor with a 0.1mm-10mm diameter. The control system preferably utilizes specific software enabling simultaneous appearance of all these three

images on the monitor. Preferably, the control system performs the so-called learning mode for each specific set of dishes. The control system can be connectable to other system(s) through any known communication protocol, for example allowing operation of the monitoring and controlling process through the Internet.

It should be noted that the simultaneous imaging of the entire dish-with-label enables real time visualization and evaluation of all the drops within the dish. The evaluation of the embryo stage includes *inter alia* the following development stages: meiosis, mitosis, number of cells within the embryo (2, 3,... 8), blastocyst, etc. Typically, each embryo is kept within the embryo-guard unit between 1 to 5 days until obtaining a desired stage in the development of the embryo such as blastocyst ready for implantation. The evaluation scheme is exemplified in **Fig. 5.** This procedure allows for comparing all the samples simultaneously with a reference sample to thereby improving the quality control of the sample development and selection of the best embryo for implantation. The remaining (non-selected) embryos may then be transferred from the incubator for storage according to any known procedures, e.g., cryopreservation. The technique of the present invention thus enables obtaining and managing of complete documentation relating to the embryo development for each subject.

The entire technique of the present invention will now be described more specifically with reference to **Fig. 6**. Patients interested in the IVF procedure are assigned with unique IDs, thereby creating matching sets (e.g., pairs) of IDs. Data indicative of the IDs are presented on labels attached to the patients and corresponding samples' containing dishes, and recorded in a central control system. The latter is also recorded with data indicative of a physician responsible for a specific procedure, who preferably utilizes a personal controller during samples' manipulation, data collection and recording. Also recorded in the central control system is data indicative of the respective matcher device (one of the plurality of matcher devices) in which matching of samples is verified. After fertilization, the fertilized eggs-containing dish is preferably assigned and labeled with an

identification code associated with the specific matching pair. The fertilized eggs-containing dish is then transferred to the embryo-guard unit for embryo development, where its development is monitored until selection of the best embryo for implantation. As indicated above, fertilization can be carried out within the embryo-guard unit. Prior to implantation, the IDs on the selected embryo containing dish and patient are again inspected for matching. Non-selected embryos are transferred to the preservation system, and may then be used for future implantation, for example in case of unsuccessful initial implantation or miscarriage.

A non-limiting example of the entire technique of the present invention, including the matcher device and the embryo-guard unit and their combined operation is detailed in the attached Annex A.

Thos skilled in the art will readily appreciate that various modifications and changes can be applied to the embodiments of the invention as hereinbefore exemplified without departing from its scope defined in and by the appended claims.

CLAIMS:

1. A system for controlling a process of biological entities matching, the device comprising:

- a holder for each of the biological entities, each holder being labeled with a unique identification code assigned to the respective biological entity;
- a matcher device having a support platform for supporting the labeled holders, and an imaging arrangement operable to acquire images of the labels, and generate data indicative thereof;
- a control system having a memory utility for storing records each representative of matching sets of biological entities' identification codes, and for storing said generated data, the control system being operable to analyze the generated data to identify the identification codes and determine whether the respective biological entities belong to a matching set.

2. A system for monitoring and controlling a process of embryo development, the system comprising an incubator including:

- a support stage for carrying at least one embryo-containing holder labeled with a unique identification code, such that the identification code and an embryo-containing site in the holder are located in an imaging plane;
- an imaging arrangement operable for imaging said unique identification code and the embryo within the respective holder, and generating data indicative thereof; and
- a control system for periodically operating said imaging arrangement and analyzing said generated data to evaluate the embryo development.

3. A label for attaching to a biological sample holder, the label carrying an identification code to be associated with the biological samples in the holder, and having a pattern defining spaced-apart sites for locating therein the biological samples.

4. A method for identifying a biological sample comprising:

- assigning a biological sample with an identification code;

- providing a biological sample to be identified, the biological sample being located within a biological sample holder, the holder being attached with a label having attached thereto an identification code;
- acquiring an image of the identification code on the label and generating data indicative thereof;
- by image processing, analyzing the identification code on the label and determining the biological sample to which the identification code is assigned.

5. A method for controlling a process of biological entities matching, the method comprising:

- labeling each biological entity containing holder with a unique identification code assigned to said biological entity;
- providing data records each representative of matching sets of the biological entities' identification codes;
- acquiring images of the identification codes on the labels and generate data indicative thereof;
- analyzing the generated data to identify the identification codes and determine whether the respective biological entities belong to a matching set.

6. A method for monitoring and controlling a process of embryo development, the method comprising:

- providing an incubator including a support stage and an imaging arrangement;
- locating at least one embryo-containing holder labeled with a unique identification code on the support stage, such that the identification code and an embryo-containing site in the holder are located in an imaging plane;
- acquiring images of said unique identification code and of the embryo within the respective holder, and generating data indicative thereof; and
- analyzing said generated data to evaluate the embryo development.

Annex A

1. Introduction

1.1 General

Observing embryos during early stage development is one of the best means for selecting the best embryo for transfer (Edward IVF pioneer).

Presently, the monitoring of embryos *in vitro* is conducted manually by embryologists. The embryos are evaluated several times a day under a stereo-microscope located outside the incubator. This method is detrimental for the preservation of optimal conditions necessary for embryo development and causes fluctuations of temperature from the optimal 37^0C, uncontrolled CO_2 environment and light exposure for approximately 10 minutes a day. In addition, when higher magnification is necessary the embryos are observed with an inverted microscope, which is normally located outside the laminar flow which increases the risk for contamination.

The Embryo-Guard is a new system which contains several microscopic CCD cameras located inside the IVF incubator, and an active matching quality control tool.

The system is designed to perform:

- On line monitoring & time laps evaluation of embryos inside the incubator.
- Improved implantation success rates by selecting embryos based on cleavage timing.
- Optimal management of IVF lab procedures
- Controlled & documented matching utilizing barcode identification.
- Complete documentation of all procedures
- On line control per procedure
- Internet compatibility
- Real time evaluation of up to 12 dishes simultaneously

- Full robotic 3D movement of CCD microscopic cameras inside the incubator
- Reduces the need to open the incubator

In addition, The Embryo-Guard "Matcher" System is a barcode controlled matching system developed to prevent mismatching during IVF procedures. The Matcher can be used as a part of the Embryo-Guard system, or as a stand-alone system. The
The Matcher system serves as an essential tool in the quality control process of the IVF procedure. The Barcode is identified using imaging and analysis of photographs taken by CCD cameras. The system enables identification of the patients through their unique Barcode.

The Embryo-Guard System includes:

- The Embryo-Guard machine installed inside the IVF incubator
- One or more "Matcher" working station units
- Portable barcode scanner, built in a hand held PC commercial system
- Cradle
- PC
- RS232 communication system and video cable
- Stickers "Consumables" with a printed Barcode

1.2 Device Description

The Embryo-Guard is designed to track an embryo located in an incubator in a continuous and automatic manner while recording the results by using images and an invariable database of Barcodes that accompany the process from initiation until the end of the process. The system is equipped with several CCD cameras which deliver images in various sizes. Starting with a view of the full Petri dish and then to a view of a single embryo the size of the monitor. The optical system is placed on a mobile optical table that is able to move along the X-Y axes and the Z-axis is intended to focus all of the lenses (x1, x4, x20) to a final magnification of X20, X80 and X 400.
The Petri dish is placed on a round rotating plate with 12 openings and is controlled by a phase control system that enables a technician to reach each and every plate

based upon the user's choice. The system enables to track each embryo on each and every Petri dish upon demand.

With computerized assistance the system can be taught of the location of each embryo by tracking the embryo, centering it on the monitor and saving the location on the invariable database. Saving the data enables work with automatic movement while repeating the cycle for each embryo. The photographs are saved the in the database.

The system that is located within the incubator is exposed to the exact same environmental conditions associated with the incubator itself, including but not limited to the temperature, the air composition and the humidity. The instrument is attached to an external control box that supplies it with a low DC voltage and communication thereof to an electronic card. The control box is affixed to a PC computer and a navigation joystick to the phase control.

The Embryo "Matcher" device is a barcode controlled matching system developed to prevent mismatching during IVF procedures. The Matcher can be used as part of the Embryo-Guard system, or as a stand-alone unit. It serves as an essential tool in the quality control process of the IVF procedure and enables linking a number of Embryo Matcher units to one central computer.

Based upon the characteristics of the designated action to be performed, the instrument operates a generic testing procedure that includes the number of components it is meant to test, and to verify the correctness of the code. The entire operative process is conducted in the petri dish, as long as it is still located outside the mother instrument, is accompanied by continuous reviewing between the petri dishes and the test tube. In the event that at some point a discrepancy should occur in the content of the barcode, the system alerts of the same by sending a notice to the Matcher screen, transmitting a record of the discrepancy to the central computer, operation of a buzzer and lighting up a flashing red LED until the problem is solved by the user. The central computer conducts a complete recording of all the barcode comparative actions from all the system units.

The Matcher system is comprised of an LCD monitor, and a small keyboard to conduct command operations from the central computer. The Petri dishes are placed at the barcode-testing phase in the Embryo Matcher system upon a surface heated to 37^0C, controlled by a microprocessor and temperature sensor. The temperature will be permanently shown on the right hand side of the screen. The sperm vials are

located in an unheated surface area. The Matcher includes Backlight surfaces based on the White LED technology. The dish and vial charging surface is located opposite an optical sensors. This indicates to the system if they are present or absent from the waiting position.

The Hand held PC kicks in to action in the event of ovum pick up or embryo implantation.

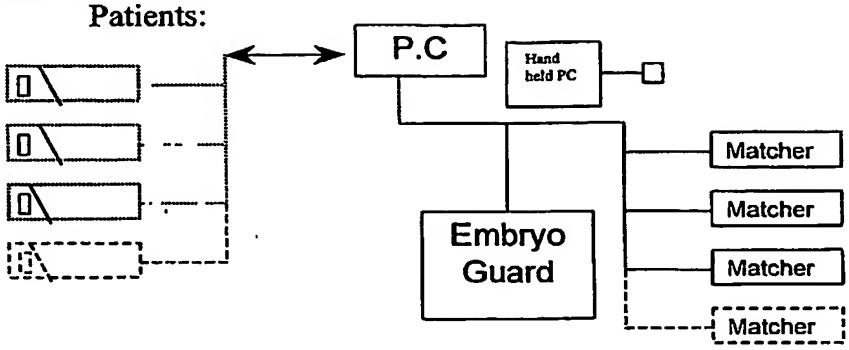
The physician scans the patient's wrist bracelet with the Hand held PC, and once a successful match is made between the code on the patient's bracelet and the data located in the Hand held PC memory, the procedure is approved. In the event of ovum pick up, a sticker with the patient's barcode identification number is attached to the back of the petri dish that is intended to be placed in the Embryo-Guard unit. The Hand held PC is returned to the Cradle and connected to the main PC. The patient's barcode is transmitted to all the system's units and from this point onwards, an external surveillance is conducted for that specific barcode. Handling of the oocytes and conducting the insemination are preformed inside the laminar flow.

Moving the dish or the test tube from the Matcher unit is immediately detected by optical sensors and transmitted to the central computer when matching is completed. The central computer transmits the data to the Matcher unit that updates the screen with the new status.

Matching Illustration

Sperm collection/ OPU/ ET

Patients:



1.3 Technical Specification

The system is composed of nine elements:

1. The body of the instrument, including *inter alia* all the mechanical and optical components in a steel kit (stainless steel).
2. A rotating plate accommodating 12 Petri dishes, 60-millimeters in diameter (aluminum).
3. An external navigation handle that includes a joystick to control the X-Y movements and an additional button to control the focus.
4. A Control Unit box that comprises the power supply and connector card.
5. Standard PC desktop computer with an image capture card
6. One or more "Matcher" units working station
7. Portable barcode scanner, built in a hand held PC commercial system

8. Cradle
9. A stickers with a printed Barcode.

The instrument is designed to work from within the incubator. The incubator shelf size is at least 48 x 48 cm under the following environmental conditions:
Static temperature reaching 37° C
CO_2 level of 5%
Oxygen control of 5%-21%
Relative humidity of ~95%
Clean Environment

The system is designed for continuous use, on a real time basis, from within the incubator. The operational cycles extends for up to 7 days per Petri dish.
Management of the 12 transparent Petri Dishes, 60mm in diameter, is conducted via the PC. Each dish is marked with a barcode sticker pursuant to the specifications and the dishes are placed in a single circle on the rotating plate.
Identification of the barcode is based upon analysis of the picture via the CCD wide-angled lens camera.
The oocyte identification system is comprised of three CCD cameras with the capability of extending to x4 and x20 lenses. The cameras are located on the optical table that moves along the three axes. The electric focus equipped with a tiny step motor is placed on the Z-axis. A Joystick unit can be used to exercise control over the focus. The background light system providing the cameras is based on the White LED technology. All three cameras are linked to one screen (monitor or PC) using an electronic multiplexer.
Control over the system's motors and peripheral components is conducted through a designated electronic card, Control over all the system's operations is exercised through an electronic control board (with an option to control the same via a PC).
The connection between the PC and the Embryo-Guard is conducted by an RS232 communication, using impermeable cables. The cables are inserted into the incubator through an opening designed specifically for the insertion of standard cables. A Composite Video line connects the Embryo-Guard to the PC Frame Grabber card. The system's power suppliers are located in the control box.

Processing Voltage:
Input – 80-250 VAC
Purveyance – 24,12,5 VDC
Average current – 2A

Size and Dimensions:
395 x 470 mm.
Height 280 mm.

The pictures are stored in a special database on the PC. The database includes all the standard database activities such as, saving, profile extraction, structured search, archive, print etc.
The system shall be operated by a designated MMI on the computer monitor.

Defining the Optical Requirements:
CCD at a size of 1/4 inch to 1/3 inch.
10-inch window on the computer monitor (based upon the user's choice).
CCD Resolution:
X4 Camera 450 TV Lines 1/3 inch
X20 Camera 330 TV Lines ¼ inch
Wide-angled camera 330 TV Lines ¼ inch.

Increments:
The increment between the CCD to the monitor will be approximately 20.
Scanning embryo locations – all the dishes will appear on the 60 mm diameter screen.
Scanning droplets – a part of a single droplet will appear on the entire monitor 1 mm in diameter. Increments of 80. Optical increment of x4
Embryo scanning – a single embryo appears on the entire screen at 0.1mm. Over-all increment of 400. Optical increment of x20. Under these increments, each embryo cell that was split into 8 parts will be approximately 40 mm in diameter.

3. Preliminary Studies

3.1 Introduction

The Embryo-Guard system is a very useful tool for evaluating embryo development. It enables us to provide the embryos with the optimal conditions necessary (37°C, 5%CO_2 and 95% humidity) without removing them from the incubator except for performing IVF related procedures. The system offers on line monitoring as well as time laps evaluation of embryos inside the incubator.

The experiments below were conducted in order to prove that the Embryo-Guard bears no influence on the development of embryos in a culture dish.

The environment in close proximity to the Embryo-Guard was tested, the influence of movement, light and the label toxicity on the embryos.

3.2 Materials & Methods

Female CB6F1 (3 weeks old) mice bred from stock (obtained from Harlan, Jerusalem, Israel) were kept under controlled conditions (12h light, 12h dark) and fed water and pellets *Teklad (*Harlan, Israel). Ovaries were stimulated by intraperitoneal injection of 0.1ml pregnant mare's serum gonadotropin (PMSG) (Sigma, St. louise, USA), and human chorionic gonadotrophin (HCG) (Sigma, St. louise, USA) 47 hours later. The females were mated with FVB/N males. Twelve hours after mating, animals were sacrificed by cervical dislocation and the ampoule was removed immediately into M2 medium (Sigma, St. louise, USA). 2PN stage embryos were flushed into a 300 µg/ml hyaloronidase (Sigma, St. louise, USA) drop. After washing the embryos three times in M2 and M16 (Sigma, St. louise, USA) they were divided into 20µl drops, each drop containing 20 embryos and cultured under mineral oil (Sigma, St. louise, USA). The dishes were placed in the EmbryoGuard in the incubator (ThermoForma 3110, Ohio, USA) at 37°C, 5%CO_2 and 95% humidity. One control group consisting of 20 embryos in 20µl drops under mineral oil was placed in the same incubator with the EmbryoGuard on a another shelf (control 1) and the second control (control 2) dish was placed in another incubator (without the Embryoguard) with the exact same environmental condition. The embryo development was evaluated every 24 hours

manually. The dishes placed in the EmbryoGuard, were rotated and pictures were taken. The temperature in the incubator was recorded using a data logger (ALMEMO 2290-4, Germany) connected to a PC.

In the dishes that were used for the sticker experiment the embryos were divided in the same manner as in the control groups (20 embryos in 20μl drops under mineral oil). The stickers were attached on the inside upper lid of the Petri dish in order to magnify the effect of the glue and inc on the embryos. The dished were placed in the incubator that did not contain the Embryoguard.

Embryonic development among different treatment groups were compared initially using Chi-square (χ^2) analysis. If significant differences existed among groups, pair-wise comparisons were made. Probabilities of treatment difference <0.05 were considered significant.

3.3 Results

The cleavage rate of 2PN embryo in the EmbryoGuard 24h after fertilization was 82% (115/140), Control group 1 was 84% (136/162), Control group 2 was 90% (197/220) and the group which tested the toxicity of the stickers was 86% (120/140). The balstocysts formation on the fifth day after fertilization was 45% (52/115), 49% (67/136), 54% (106/197) and 58% (70/120), respectively. (Table. 1)

Table 1: Embryo development

Treatment	Total 2PN	Cleavage rate ±S.E (N)	Blastocyst rate±S.E (N) ***
EmbryoGuard	140	82%±3.2 (115)	45%±4.6 (52)
*Control 1	162	84%±2.8 (136)	49%±4.2 (67)
**Control 2	220	90%±2.0 (197)	54%±3.5 (106)
Sticker	140	86%±2.9 (120)	58%±4.5 (70)

* Using the same incubator with the EmbryoGuard on another shelf.
** Using another incubator with the exact same environmental condition as the EmbryoGuard incubator.
*** Blastocyte rate out of cleaving embryos.

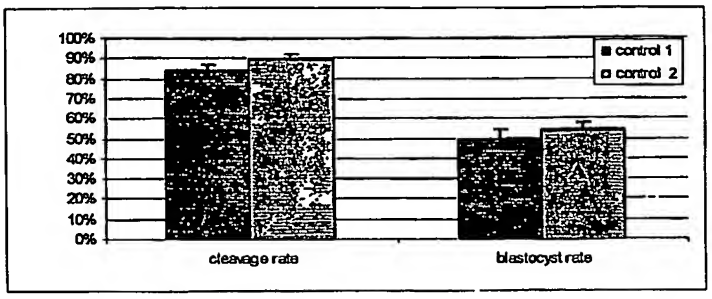


Fig. 1 comparison between control 1 and control 2

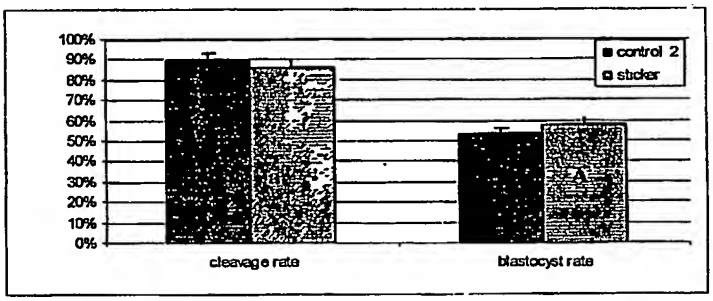


Fig. 2 comparison between control 2 and the sticker group

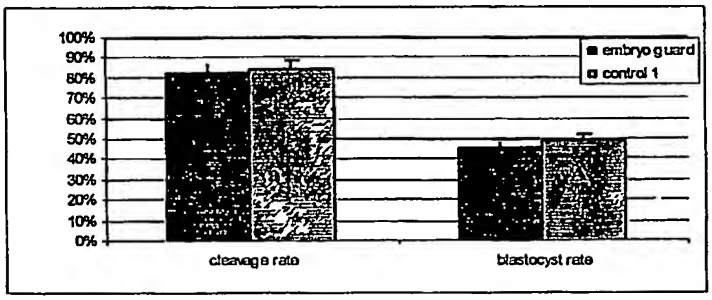


Fig. 3 comparison between control 1 and the EmbryoGuard group

The temperature remained steady throughout the entire experiment in the EmbryoGuard incubator 36.7°C ±0.2. (Fig.4)

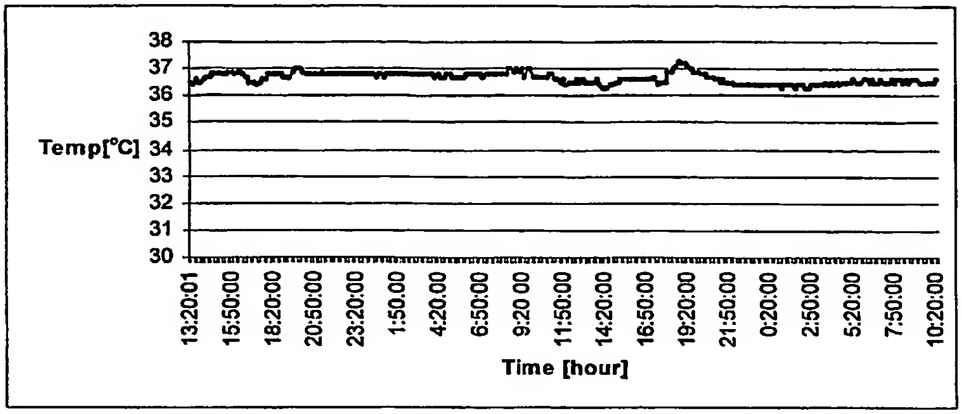


Fig.4- Temperature recording

3.4 Conclusions

Results from a previous experiment (Arav *et al* ICAR 2000) using CCD cameras for continues evaluation of balstocysts and an appropriate background light source inside an incubator, correlate with our last experiments which showed normal cleaving development that does not differ from both control groups – one in the same incubator and the other in another with the exact same conditions. Analysis of results obtained, showed that there were no significant differences ($P<0.05$) between the control groups (Fig. 1) throughout the entire embryonic development. This confirms that the environmental conditions in the incubator consisting of the EmbryoGuard unit where not disturbed. When comparing control 1 group to the EmbryoGuard group (Fig. 3) the embryos continued to develop to the blastocyst stage, with no significant differences. The sticker group consistently, did not show lower development than control group 2 (fig. 2) which incubated in the same incubator.

It is thus concluded that neither the illumination nor any source of light radiation affects the embryos growth. A suitable incubation environment was maintained while the Embryo-Guard unit operated within the incubator. There were no temperature fluctuation and the gas circulation was not impaired (Fig. 4). The fact that the

stainless steel plate rotated during the automatic evaluation process, did not affect the embryos. The labels (glue and inc) were also not found to have a toxic affect on the embryos (Table 1).

4. Risk analysis

Risks associated with the use of the EmbryoGuard includes those risks associated with the IVF process as well as additional risks related to the use of the EmbryoGuard.

Risk analysis of the EmbryoGuard unit indicates towards two main factors – the light and the sterilization processes.

All efforts were made to minimize these risks by using all possible means of sterilization and by selecting the means of illumination that are less than the common practice that is used today in the labs during routine IVF process.

4.1 Illumination

Cold and warm light sources are used for the intensive illumination of different kinds of objects. Although there is very little knowledge of the effect of illumination on embryos the common assumption is that light does have an effect on embryo development. Nevertheless time laps videoing, including continuous illumination was used in several studied without causing major damage (Arav *et al* ICAR 2000).

4.1.1 Luminous Intensity

The intensity of light used in a microscope is 600lm (lumen), the equivalent of 35 Watts. In comparison the white LED light used in the EmbryoGuard system is 9200 mcd (Millicandela's), which is equivalent to approximately 60mW (MilliWatt). This figure correlates with the width of a light beam coming from a 20° direction.

These facts make it clear that the intensity of light used in the EmbryoGuard is lower than light emitted from a microscope and thus it helps maintain the embryos in optimal conditions.

4.1.2 Type of light

The wave length spectrum that is visible to the human eye from light emitted through a microscope varies between 450 nm and 750 nm. This is the same wavelength as is emitted from the white LED light installed in the EmbryoGuard unit.

4.1.3 Length of exposure

Currently, the monitoring of embryos is conducted manually by embryologists. The embryos are removed from the incubator 1-3 times a day for evaluation. This exposes them to light for approximately 10 minutes a day. The Embryo-Guard unit minimizes the embryos exposure to light as they are only exposed to light for 30 seconds a day (in the case they are photographed 3 times a day).

The general effect of exposure to light has not yet been determined, however use of the Embryo-Guard unit significantly decreases the exposure of the embryos to light and it's possibly harmful effects.

4.2 Sterility

Prior to placing the Embryo-Guard unit in the incubator it must be sterilized in order to maintain a clean and sterile environment. The system is delivered to the customer's laboratory when it is sealed and ready for use.

The Embryo-Guard is composed of anodized stainless still. Therefore the following six sterilization steps are carried out before delivery to ensure sterility of the device:

1) Wipe of the interior elements with 70% ethanol.
2) Ultra Violet radiation of the device body and the lid separately for an hour.
3) Assembly of the lid and the body in a clean environment (laminar flow).
4) Wipe again with 70% ethanol
5) Transfer of the Embryo-Guard unit in a sealed nylon bag to the investigational site.
6) Wipe again with 70% ethanol prior to installing the Embryo-Guard in the investigational incubator.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: AMIR ARAV

Serial No.: Group No.:

Filed: OCTOBER 10, 2002 Examiner:

For: METHOD AND SYSTEM FOR CONTROLLING THE BIOLOGICAL SAMPLES DEVELOPMENT

Attorney Docket No.: U014254-3

Assistant Commissioner for Patents
Washington, D.C. 20231

WRITTEN ASSERTION OF SMALL ENTITY STATUS

This is written assertion on the basis of:

☐ personal knowledge;

☐ applicant's letter of _____;

☐ applicant's agent's letter of _____; or

☒ e-mail of October 10, 2002

by a practitioner (not necessarily of record) that the above application is entitled to small entity status and, therefore, fees.

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Date: October 10, 2002

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SUE DARGENIO
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"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will not be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.

NOTE: "To establish small entity status after the payment of the basic filing or national stage fee as a non-small entity, a written assertion of small entity status is required to be submitted." Notice of September 8, 2000, 65 Fed. Reg. 54604, at 54609.

NOTE: 37 C.F.R. § 1 27(c)(1)· "Assertion by writing. Small entity status may be established by a written assertion of entitlement to small entity status. A written assertion must:

(i) Be clearly identifiable;

(ii) Be signed (see paragraph (c)(2) of this section); and

(iii) Convey the concept of entitlement to small entity status, such as by stating that applicant is a small entity, or that small entity status is entitled to be asserted for the application or patent. While no specific words or wording are required t assert small entity status, the intent to assert small entity status must be clearly indicated in order to comply with the assertion requirement."

NOTE: 37 C.F.R. § 1.27(c)(2): "Parties who can sign and file the written assertion. The written assertion can be signed by:

(i) One of the parties identified in § 1.33.(b) (e.g. an attorney or agent registered with the Office). § 3.73(b) of this chapter notwithstanding, who can also file the written assertion;

(ii) At least one of the individuals identified as an inventor (even though a § 1.63 executed oath or declaration has not been submitted), notwithstanding § 1.33(b)(4), who can also file the written assertion pursuant to the exception under § 1.33(b) of this part; or

(iii) An assignee of an undivided part interest, notwithstanding §§ 1.33(b(3) and 3.73(b) of this chapter, but the partial assignee cannot file the assertion without resort to a party identified under § 1.33(b) of this part."

35 C.F.R. § 1.33(b):
(b) Amendment and other papers. Amendments and other papers, except for written assertions pursuant to § 1.27(c)(2)(ii) of this part, filed in the application must be signed by.

(1) A registered attorney or agent of record appointed in compliance with § 1.34(b);

(2) A registered attorney or agent not of record who acts in a representative capacity under the provisions of § 1.34(a);

(3) An assignee as provided for under § 3.71(b) of this chapter; or

(4) All of the applicants (§ 1.41(b)) for patent, unless there is an assignee of the entire interest and such assignee has taken action in the application in accordance with § 3.71 of this chapter.

Respectfully submitted,

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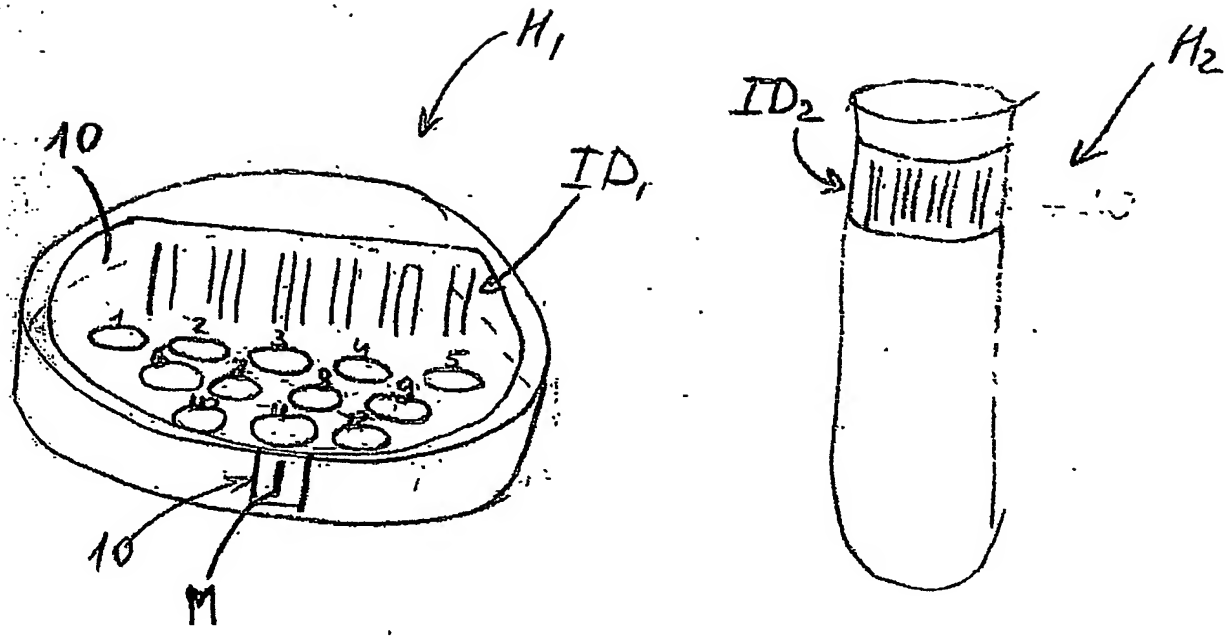
26 West 61st Street
New York, N. Y. 10023
Reg. No.: 25,858 (212) 708-1930


H1
10
ID1
1
2
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5
6
7
8
9
10
11
12
10
M
ID2
H2

Fig. 1

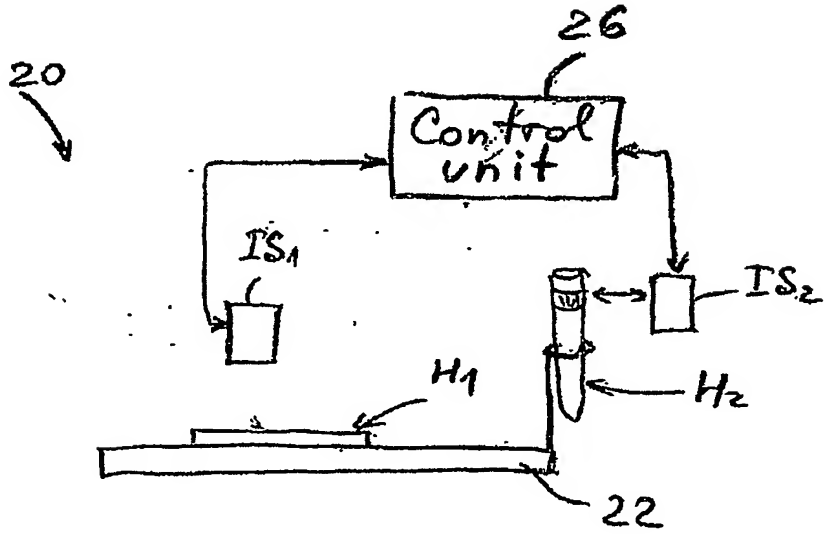
20
26
Control unit
IS1
IS2
H1
H2
22

Fig. 2

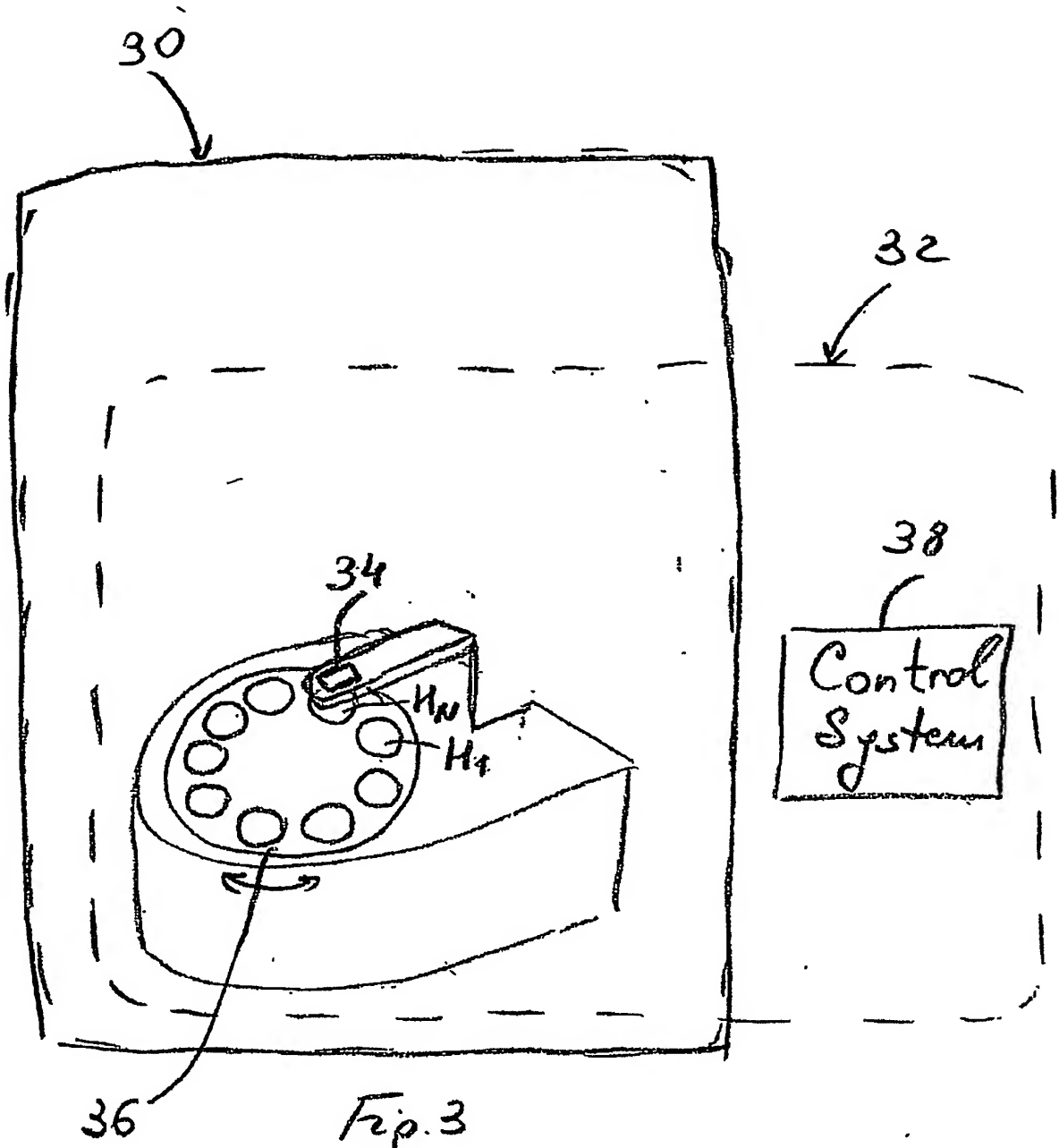

Fig. 3

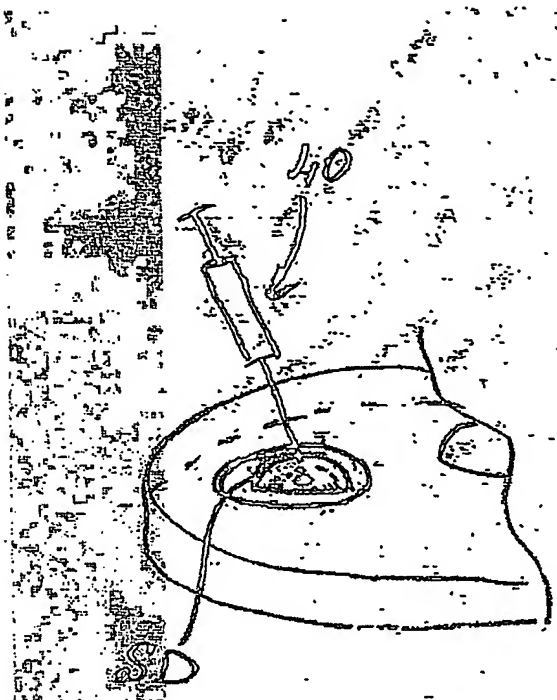

Fig. 4

Fig. 5

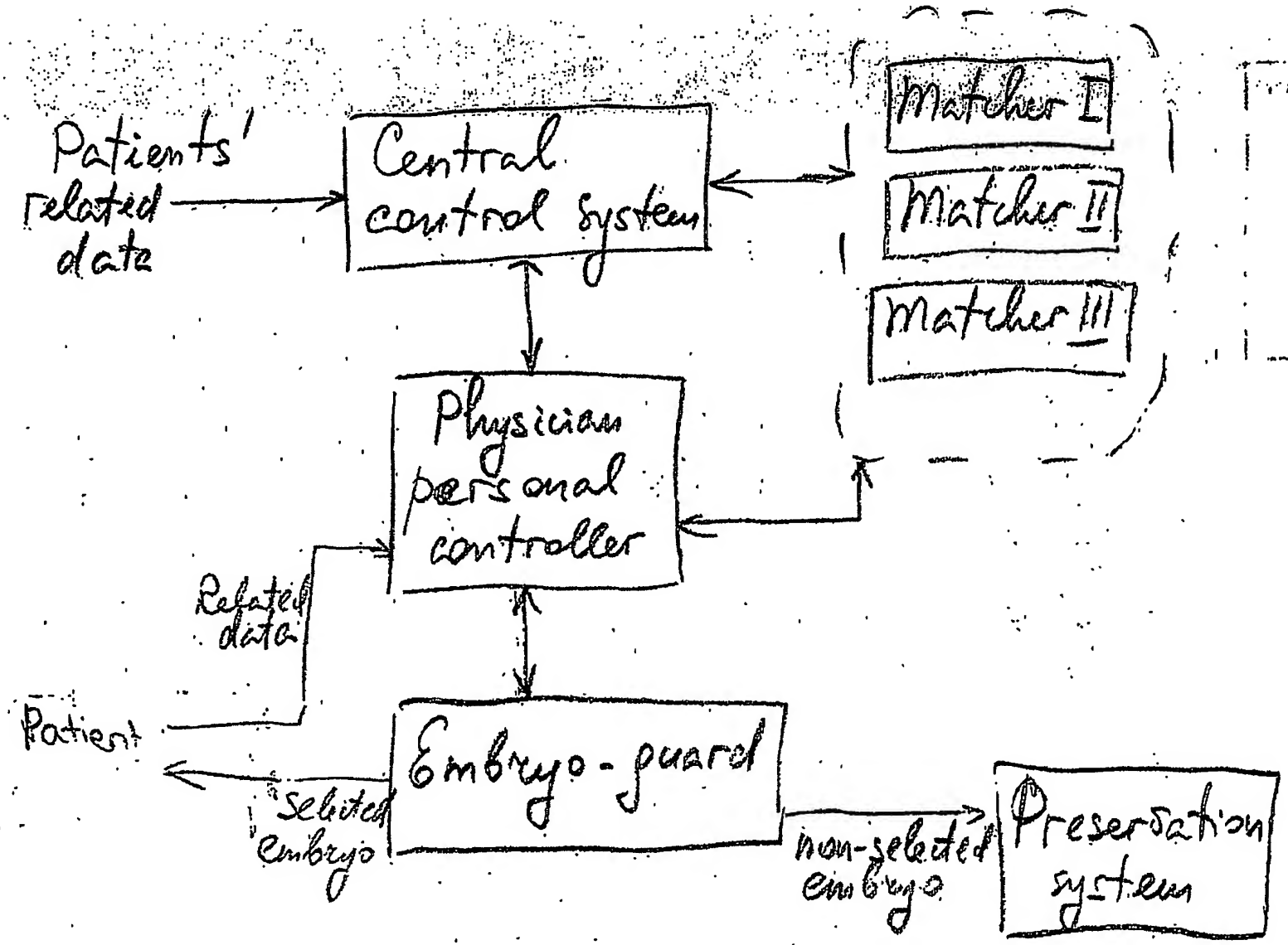

Fig. 6